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10/522,370	05/03/2005	Karl Stangl	2958-130	1382

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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
NIEBAUER, RONALD T	

ART UNIT	PAPER NUMBER
1609	

NOTIFICATION DATE	DELIVERY MODE
06/28/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,370	STANGL ET AL.	
	Examiner	Art Unit	
	Ronald T. Niebauer	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the following species: disease type – cardiac; fibrosis cause – pressure stress in arterial hypertension; proteasome inhibitor – threonine protease inhibitor MG132, in the reply filed on 4/25/07 is acknowledged. The traversal is on the ground(s) that the reference does not teach the claimed invention. This is not found persuasive. Applicants claim that 'proteasome inhibitors as in the present invention are not inhibitors of a serine protease'. However applicants claim (original claim 8 and current claim 23) that the proteasome inhibitor is a serine protease inhibitor. Further, the broad scope of original claim 1 does not recite that the inhibitors of the present invention are not inhibitors of a serine protease. The arguments are not drawn to the generic, independent claim. Section 1801 of the MPEP states:

> Unity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims.

Further, Schubert et al. (US2004/0106539 see 102 rejection below) teaches the claimed invention showing that no contribution is made over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent

Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The application, for example claim 26 (Tyr-Leu_3-VS; Ada-Lys(Bio)-Ahx_3-Leu_3-VS; and Ac(Me)-Ile-Ile-Thr-Leu-EX) contains sequences of four or more L-amino acids which require a sequence listing as set forth in 37 C.F.R. 1.821 - 1.825.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Specification

The disclosure is objected to because of the following informalities: in numerous locations (for example page 4 line 28, 32; page 8 table 1; page 14 line 5-8) numerical values are used in which a comma separates the numbers while it would seem that a period should be used instead of the comma (for example 0,5 is used instead of 0.5).

Appropriate correction is required.

Claim Objections

Claims 14 and 21 are objected to because of the following informalities: abbreviations (such as ACE, MG132) are used without a clear definition of the meaning of the abbreviation in the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 14-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 and dependent claims 15-26 are drawn to a method for treating fibrotic diseases which are not caused by inflammatory responses to foreign matters. In this context the term 'foreign matters' is unclear. Due to this lack of clarity the breadth of the claim is unclear. What is the patient population and what type of fibrotic diseases are to be treated? The only guidance given in the specification (page 9 line 22) implies that foreign matter is silicone. After reading the specification it is not clear whether or not fibrotic diseases which develop after infection are considered 'caused by inflammatory responses to foreign matters'. Hence, the meets and bounds of these claims are unclear.

Claim 14 is drawn to a method wherein said cardiac fibrosis is treatable with particular inhibitors/antagonists. It is unclear based on the claim language if the treatment agents are part of the method or if the agents are only used to further define properties of the fibrosis.

Claim 21 is drawn to a method wherein the inhibitor is a low-molecular organic compound. Does 'low-molecular' refer to the molecular weight of the compound or to something else?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21,23,25,26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious,"

and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are briefly drawn to a method of treatment comprising administering at least one proteasome inhibitor. Claim 21 recites a 'modified peptide inhibitor', claim 23 recites a 'binding protein' and 'a gene expression inhibitor of the proteasomal system', claim 25 recites 'an antibody or binding-reactive part or derivative thereof', claim 26 recites 'an anti-sense-RNA or a double-stranded RNA (dsRNA) against a proteasome encoding sequence'

and 'a triplex forming oligonucleotide against a proteasome encoding sequence' and 'a knock-out construct against a proteasome encoding sequence'.

(1) Level of skill and knowledge in the art:

The level of skill in the art is high with regards to synthesis of proteasome inhibitors, the knowledge in the art is low with regards to the knowledge of the structure of a 'modified peptide inhibitor' (claim 21); a 'binding protein' and 'a gene expression inhibitor of the proteasomal system' (claim 23); an 'antibody or binding-reactive part or derivative thereof' (claim 25); 'an anti-sense-RNA or a double-stranded RNA (dsRNA) against a proteasome encoding sequence' and 'a triplex forming oligonucleotide against a proteasome encoding sequence' and 'a knock-out construct against a proteasome encoding sequence' (claim 26).

(2) Partial structure:

Examples of proteasome inhibitors are disclosed (page 3 line 4). However, sufficient examples of the recited 'modified peptide inhibitor' (claim 21); a 'binding protein' and 'a gene expression inhibitor of the proteasomal system' (claim 23); an 'antibody or binding-reactive part or derivative thereof' (claim 25); 'an anti-sense-RNA or a double-stranded RNA (dsRNA) against a proteasome encoding sequence' and 'a triplex forming oligonucleotide against a proteasome encoding sequence' and 'a knock-out construct against a proteasome encoding sequence' (claim 26) have not been provided.

(3) Physical and/or chemical properties and (4) Functional characteristics:

A 'modified peptide inhibitor' (claim 21) is recited, but the properties and characteristics associated with the modification have not been provided. A 'binding protein' and 'a gene expression inhibitor of the proteasomal system' (claim 23) is recited, but the properties and

characteristics have not been provided nor is the structure evident from the function. An 'antibody or binding-reactive part or derivative thereof' (claim 25) is recited but the properties and characteristics of a binding-reactive part or derivative thereof have not been provided. 'An anti-sense-RNA or a double-stranded RNA (dsRNA) against a proteasome encoding sequence' and 'a triplex forming oligonucleotide against a proteasome encoding sequence' and 'a knock-out construct against a proteasome encoding sequence' (claim 26) are recited but the properties and characteristics have not been provided nor is the structure evident from the function.

(5) Method of making the claimed invention:

The synthesis of the proteasome inhibitors has not been provided.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 21,23,25,26 is/are broad, with respect to all possible compounds encompassed by the claims. The possible structural variations for certain compounds are limitless to any modified peptide inhibitor/binding protein/antibody derivative. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description of compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*,

736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 11, 18-19, 21-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Schubert et al. (US 2004/0106539).

Briefly, claim 11 is drawn to a method of treatment and dependent claims 21-26 identify a particular inhibitor for the treatment.

Schubert teach the use of proteasome inhibitors for affecting the ubiquitin/proteasome pathway (abstract). In particular, the proteasome inhibitor compositions are disclosed for treatments, particularly for a patient population with liver cirrhosis/fibrosis (section 0002). Liver fibrosis falls within the claim limitation of diseases 'not caused by inflammatory response to

foreign matters' (see 112 2nd paragraph rejection above). Particular proteasome inhibitors such as MG132, a threonine protease inhibitor/peptide aldehyde (section 0013) are taught (section 1.2 beginning with section 0013).

Claims 11-14,18-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Pluenneke (US 2003/0148955).

Briefly, claim 11 is drawn to a method of treatment and dependent claims 18-20 identify particular diseases that are treated. Claims 12-14 are briefly drawn to a method for treating cardiac fibrosis.

Pluenneke teach a combination treatment via a TNFalpha inhibitor and a proteasome inhibitor (section 0056). This combination meets the claim limitations since the comprising language used in the claim is open to combinations. Pluenneke teach treating organ fibrosis diseases (section 0070) such as that of the liver. Pluenneke also teach that cardiovascular disorders are treatable with the combination therapy (section 0046), specifically myocardial infarction (section 0046) and hypertension (section 0052). Further, it is well-known that myocardial infarction and hypertension have been treated with ACE inhibitors.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2003/0148955).

Briefly the claims are drawn to a method of administering a specific dose of a proteasome inhibitor.

As discussed above, Pluenneke teach a combination treatment via a TNFalpha inhibitor and a proteasome inhibitor (section 0056). This combination meets the claim limitations since the comprising language used in the claim is open to combinations. Pluenneke teach treating organ fibrosis diseases (section 0070) such as that of the liver. Pluenneke does not teach the specific doses recited in the claims of the current invention.

One would have been motivated to determine an optimal dosage because Pluenneke teach that appropriate doses of the inhibitors can be determined by the animal's body weight (section 0089), and standard dosing trials (section 0029).

It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g.dosages), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

One would have reasonable expectation for success since proteasome inhibitors have been used in treatments previously and Pluenneke mentions that doses of the inhibitors can be determined.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Application 10/522,706 which shares common inventors is noted of interest. The current claims do not necessitate a double patenting rejection but the application is cited of interest.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ronald T. Niebauer whose telephone number is 571-270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mary Mosher can be reached on 571-272-0906. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rtn

MARY MOSHER
SUPERVISORY PATENT EXAMINER

6-22-07

Notice to Comply	Application No. 10522370	Applicant(s) STANGL ET AL.	
	Examiner Niebauer, Ronald T.	Art Unit 1609	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The application, for example claim 26 (Tyr-Leu$_3$-VS; Ada-Lys(Bio)-Ahx$_3$-Leu$_3$-VS; and Ac(Me)-Ile-Ile-Thr-Leu-EX) contains sequences of four or more L-amino acids which require a sequence listing as set forth in 37 C.F.R. 1.821 - 1.825.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-0731 or (571) 272-0951
For CRF Submission Help, call (571) 272-2510
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